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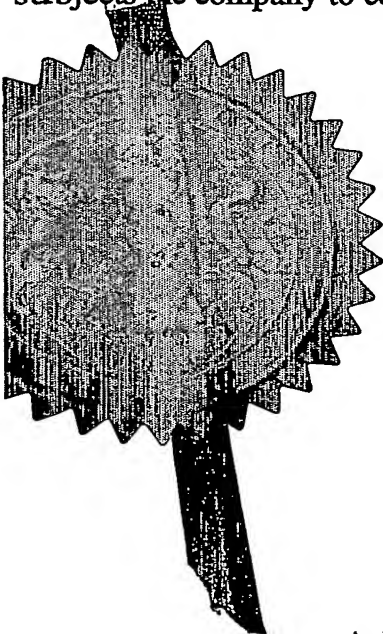
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0209539.6

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26APR02 E714147-1 D02944  
P01/7700 0.00-0209539.6

Patents ADP number (if you know it)

07764137001

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GB

Title of the invention

MONOMER, POLYMER AND PROCESS

Name of your agent (if you have one)

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which all correspondence should be sent  
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APPLICANTS

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TITLE

MONOMER, POLYMER AND PROCESS

## MONOMER, POLYMER AND PROCESS

The present invention relates to a process for the synthesis of polymers which are useful as supports in solid phase organic synthesis (SPOS) and to intermediates for use therein.

PCT/GB99/02193 discloses a series of novel polymer resin supports which find use as supports in solid phase organic synthesis (SPOS).

These polymer resins are of commercial importance and there exists a need for improved methods for their synthesis. We have found that certain novel monomers and resins find use in improved routes to these polymers.

According to a first aspect of the present invention there is provided a monomer which comprises a protected hydroxypolyC<sub>2-4</sub> alkyleneoxy chain attached to a polymerisable unit wherein the protected hydroxypolyC<sub>2-4</sub> alkyleneoxy chain contains from 2 to 10 C<sub>2-4</sub> alkyleneoxy groups and wherein the hydroxypolyC<sub>2-4</sub> alkyleneoxy chain is protected with an optionally substituted trityl group.

The hydroxypolyC<sub>2-4</sub>alkyleneoxy chains attached to the monomer according to the present invention are often selected from hydroxypolyethyleneoxy (HO(CH<sub>2</sub>CH<sub>2</sub>O)<sub>2-10</sub>-), hydroxypolypropyleneoxy (HO(CH<sub>2</sub>CH(CH<sub>3</sub>)O)<sub>2-10</sub>-) and hydroxypolybutyleneoxy (HO(CH<sub>2</sub>CH(C<sub>2</sub>H<sub>5</sub>)O)<sub>2-10</sub>-) chains. In a preferred embodiment of the invention the hydroxypolyC<sub>2-4</sub>alkyleneoxy chain is hydroxypolyethyleneoxy.

The number of C<sub>2-4</sub>alkyleneoxy groups in the hydroxypolyC<sub>2-4</sub>alkyleneoxy chain can range from 2 to 10, but is preferably from 2 to 8 and more preferably from 3 to 5. Most preferably, there are four C<sub>2-4</sub>alkyleneoxy groups in the hydroxypolyC<sub>2-4</sub>alkyleneoxy chain.

In a highly preferred embodiment of the invention the hydroxypolyC<sub>2-4</sub>alkyleneoxy chain is hydroxytetraethyleneoxy (HO(CH<sub>2</sub>CH<sub>2</sub>O)<sub>4</sub>-).

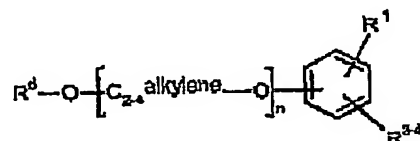
The polymerisable unit of the monomer according to the present invention is often selected from optionally substituted styrenes, acrylates and acrylamides. In a preferred embodiment of the invention the polymerisable unit is an optionally substituted styrene, optionally substituted methylstyrene, optionally substituted ethyl (meth)acrylate, optionally substituted propyl (meth)acrylate or optionally substituted N-methyl (meth)acrylamide.

In a highly preferred embodiment of the invention the polymerisable unit is an optionally substituted styrene or optionally substituted methylstyrene.

Where the polymerisable unit is an optionally substituted styrene or optionally substituted methylstyrene, the phenyl ring of the styrene is preferably optionally substituted by 1 or 2 substituents often selected from methyl, ethyl, propyl, fluoro, chloro and bromo.

Optionally substituted trityl groups include triphenylmethyl [trityl], di-methoxyphenylphenylmethyl [dimethoxy trityl], methoxyphenyl-di-phenylmethyl [monomethoxy trityl], and 2-chlorophenyldi-phenylmethyl [2-chlorotrityl] groups.

In a most preferred embodiment of the invention, the monomer is a compound of formula (1)



wherein

$R^1$  is an optionally substituted ethylene group;

$R^{2-4}$  are independently hydrogen, hydrocarbyl, halogen, or hydrocarbyloxy;

$R^5$  is an optionally substituted trityl group; and

$n$  is 2 to 10.

Preferably,  $R^1$  is a  $CH=CH_2$ ,  $CH=CHCH_3$ , or  $C(CH_3)=CH_2$  group. Most preferably,

$R^1$  is a  $CH=CH_2$ .

Preferably, the  $R^5-O-[C_{2-4}alkylene-O]_n$  group is para to  $R^1$ .

Preferably,  $[C_{2-4}alkylene-O]_n$  is  $[-CH_2CH_2O-]_n$ ,  $[-CH_2CH(CH_3)O-]_n$  or  $[-CH_2CH(C_2H_5)O-]_n$ . Most preferably  $[-CH_2CH_2O-]_n$ .

Preferably  $n$  is 2 to 8, more preferably  $n$  is 3 to 5. Most preferably  $n$  is 4.

Preferably  $R^{2-4}$  are all hydrogen.

Hydrocarbyl includes alkyl, aryl, alkaryl and aralkyl groups. Preferable when any of  $R^{2-4}$  are hydrocarbyl or hydrocarbyloxy groups the hydrocarbyl is an alkyl group, most preferably  $C_{1-4}$  alkyl group.

The monomers according to the first aspect of the present invention are useful in polymerisation reactions to form resins from which the polymer supports disclosed in PCT/GB98/02193 can be obtained.

Accordingly, a second aspect of the present invention provides a process for the preparation of a polymer support comprising polymerisation of a monomer comprising a protected hydroxypoly $C_{2-4}$  alkyleneoxy chain attached to a polymerisable unit wherein the protected hydroxypoly $C_{2-4}$  alkyleneoxy chain contains from 2 to 10  $C_{2-4}$  alkyleneoxy groups and wherein the hydroxypoly $C_{2-4}$  alkyleneoxy chain is protected with an optionally substituted trityl group, under conditions to produce cross-linking.

The monomer comprising a protected hydroxypoly $C_{2-4}$  alkyleneoxy chain, attached to a polymerisable unit wherein the protected hydroxypoly $C_{2-4}$  alkyleneoxy chain contains from 2 to 10  $C_{2-4}$  alkyleneoxy groups and wherein the hydroxypoly $C_{2-4}$  alkyleneoxy chain is protected with an optionally substituted trityl group can be as described above in the first aspect of the present invention.

Optionally, in the process of the present invention the monomer comprising a protected hydroxypolyC<sub>2-4</sub> alkyleneoxy chain attached to a polymerisable unit wherein the protected hydroxypolyC<sub>2-4</sub> alkyleneoxy chain contains from 2 to 10 C<sub>2-4</sub> alkyleneoxy groups and wherein the hydroxypolyC<sub>2-4</sub> alkyleneoxy chain is protected with an optionally substituted trityl group may comprise a mixture of isomers.

Preferably, when a mixture of isomers is used in the process of the present invention, the monomer is a compound of formula (1). Most preferably, the monomer is a mixture of isomers wherein R<sup>6</sup>O-[-C<sub>2-4</sub>alkylene-O]<sub>n</sub> group and R<sup>1</sup> occupy isomeric positions on the phenyl ring

Preferably, in the process of the present invention, the monomer comprising a protected hydroxypolyC<sub>2-4</sub> alkyleneoxy chain attached to a polymerisable unit is co-polymerised in the presence of a cross linking monomer.

The extent of cross linking in the polymers is determined by the concentration of cross linking monomer in the polymerisation reaction. Generally the weight % of cross-linking monomer is in the range of from 0.1 to 70%, commonly from 0.5 to 20%, such as from 1 to 10%, and most preferably no more than 6% by weight. Polymers comprising no more than 20% by weight of cross-linking monomer are generally swellable, whilst polymers comprising greater than 20% of crosslinking monomer are generally not swellable.

Suitable cross-linking monomers include divinyl benzene (DVB) or multifunctional (meth)acrylates such as di/tri acrylates or di/tri methacrylates such as ethylene glycol diacrylate, ethylene glycol dimethacrylate, trimethylpropane trimethacrylate, trivinylbenzene or N,N'-bis-acryloyl ethylene diamine. Preferably the cross-linking monomer is DVB.

Preferably 0.5 to 5% by weight of DVB is used. Most preferably 1 to 3% by weight DVB is used.

Optionally, in the process of the present invention, the monomer comprising a protected hydroxypolyC<sub>2-4</sub>alkyleneoxy chain attached to a polymerisable unit is co-polymerised in the presence of one or more monomers selected from styrenes, for example styrene, hydroxystyrene, methylstyrene, hydroxymethylstyrene and chloromethylstyrene, esters of acrylic acid and esters of (meth)acrylic acid, for example methyl acrylate, ethyl acrylate, methyl methacrylate, ethyl acrylate, hydroxyethyl (meth)acrylate and hydroxypropyl (meth)acrylate, and acrylamides, for example N-methyl acrylamide and N-methylol (meth)acrylamide; wherein the phenyl ring in the styrenes is optionally substituted by 1 or 2 substituents often selected from methyl, ethyl, propyl, fluoro, chloro and bromo and wherein hydroxy groups, especially phenolic hydroxy groups, which may be present in the monomers are optionally protected and may subsequently be deprotected.

In a preferred process of the present invention, the monomer comprising a protected hydroxypolyC<sub>2-4</sub> alkyleneoxy chain attached to a polymerisable unit wherein the protected hydroxypolyC<sub>2-4</sub> alkyleneoxy chain contains from 2 to 10 C<sub>2-4</sub> alkyleneoxy groups and wherein the hydroxypolyC<sub>2-4</sub> alkyleneoxy chain is protected with an optionally substituted trityl group is co-polymerised in the presence of one or more cross linking monomers, and one or more monomers selected from styrenes, esters of acrylic acid and esters of (meth)acrylic acid, or acrylamides.

In a highly preferred process of the present invention, the monomer comprising a protected hydroxypolyC<sub>2-4</sub> alkyleneoxy chain attached to a polymerisable unit wherein the protected hydroxypolyC<sub>2-4</sub> alkyleneoxy chain contains from 2 to 10 C<sub>2-4</sub> alkyleneoxy groups and wherein the hydroxypolyC<sub>2-4</sub> alkyleneoxy chain is protected with an optionally substituted trityl group is co-polymerised in the presence of DVB and styrene.

When the polymer support is produced by polymerisation of a mixture of monomers comprising the monomer comprising a protected hydroxypolyC<sub>2-4</sub> alkyleneoxy chain attached to a polymerisable unit wherein the protected hydroxypolyC<sub>2-4</sub> alkyleneoxy chain contains from 2 to 10 C<sub>2-4</sub> alkyleneoxy groups and wherein the hydroxypolyC<sub>2-4</sub> alkyleneoxy chain is protected with an optionally substituted trityl group, and one or more monomers selected from styrenes, esters of acrylic acid and esters of (meth)acrylic acid, or acrylamides, the weight percentage of the monomer comprising a protected hydroxypolyC<sub>2-4</sub> alkyleneoxy chain attached to a polymerisable unit of the total weight of the monomers present is preferably in the range of from 1-99%, more preferably in the range of from 5-80% and most preferably from 15% to 70%.

The process of the present invention is preferably carried out by aqueous suspension polymerisation. The monomers are suspended as droplets (1-1000µm) in water. Stabilisers are usually added to prevent agglomeration of the droplets, for example polyvinyl alcohol, polyacrylic acid, polyvinyl pyrrolidone, polyalkylene oxide, barium sulphate, magnesium sulphate or sodium sulphate. The suspension is also normally stirred to maintain the suspension.

Optionally, organic non-water miscible solvents may be used in the polymerisation process. Organic non-water miscible solvents may assist droplet formation in aqueous suspension polymerisation, or may act as porogens.

Optionally inorganic salts may be added to the aqueous phase in aqueous suspension polymerisation. Inorganic salts may assist droplet formation by suppressing monomer solubility in the aqueous medium.

A free radical initiator is preferably used to initiate polymerisation. The type of initiator will generally be selected based on the monomers used. Examples of preferred free radical initiators include benzoyl peroxide, dioctanoyl peroxide, 2,2'-azobisisobutyronitrile and 2,2'-azobis(2,4-dimethylvaleronitrile).



Polymerisation is typically assisted by heating the mixture in the range of 15°C to 160°C, preferably 50°C to 90°C. It will be recognised that the temperature to which the mixture can be heated depends upon the type of monomer and initiator employed.

The resultant polymer may then be washed with suitable solvents such as tetrahydrofuran, methanol and water, dried and bead size classified, for example, by sieving.

Accordingly a further aspect of the present invention provides a polymer support which comprises protected hydroxypolyC<sub>2-4</sub> alkyleneoxy chains attached to a cross-linked polymer wherein the protected hydroxypolyC<sub>2-4</sub> alkyleneoxy chain contains from 2 to 10 C<sub>2-4</sub> alkyleneoxy groups and wherein the hydroxypolyC<sub>2-4</sub> alkyleneoxy chains are protected with an optionally substituted trityl group.

Preferably, the polymer support of the present application is obtainable by the process of the second aspect of the present invention.

The invention, in its broadest aspect, relates to the particular polymer supports however prepared.

The optionally substituted trityl group may subsequently be removed to give the cross-linked polymer containing free hydroxy groups.

Methods appropriate for removal of the optionally substituted trityl group include, for example, acid-hydrolysis. Commonly a mixture of trifluoroacetic acid in methylene chloride can be employed. The reader is referred to Advanced Organic Chemistry, 4<sup>th</sup> Edition, by Jerry March, published by John Wiley & Sons 1992, for general guidance on reaction conditions and reagents.

Preferably, when the protecting groups are removed the resulting polymer support has from about 0.1 to about 5 meq free hydroxy groups per gram of polymer.

Cross-linked polymers containing a free hydroxy group are usually produced as beads which range in size from 10µm to 2000µm. Preferably the bead size is from 50µm to 1000µm and most preferably from 75µm to 600µm. The cross-linked polymer beads are generally produced by an aqueous suspension polymerisation process, for example see Journal of Applied Polymer Science, 1982, 27, 133-138, incorporated herein by reference.

The polymer support obtained when the protecting groups are removed from the support according to the present invention has a hydroxy functionality of from 0.1 to about 5, for example up to 4.8 meq (milliequivalents) of hydroxy per gram of polymer, and often from 0.5 to 3.5, commonly 1.0 to 3.3 meq per gram for example from 1.5 to 3 meq per gram of polymer. In many embodiments, the polymer support obtained when the protecting groups are removed have from 0.5 to 2 meq of hydroxy per gram of polymer.

The invention will now be described, without limitation, by the following examples in which, unless otherwise stated:-

- a) FT-IR spectra were obtained using swollen gels in dichloromethane held between sodium chloride plates, and an ATI Genesis (Matteson) spectrometer.
- b)  $^{13}\text{C}$  magic angle (MAS) NMR spectra were obtained using solvent swollen gels in the rotor of a Bruker MAS probe on a 400MHz NMR spectrometer.
- c) yields are given for illustration and are not necessarily the maximum attainable.
- d) the following abbreviations have been used: THF = tetrahydrofuran, DMF = N,N-dimethylformamide, FMOC = fluorenylmethoxycarbonyl, PEG = polyethyleneglycol and THP = tetrahydropyranyl.

### Examples

#### **Preparation of trityl-tetraethyleneglycoxystyrene**

##### **STAGE 1**

Tetraethyleneglycol (174g, 0.9mol) was placed in a 3 necked round bottom flask fitted with a thermometer and reflux condenser. Pyridine (11cm<sup>3</sup>, 0.135mol) was added to the mixture stirred. Triphenylmethylchloride (25g, 0.09mol) was dissolved in toluene (30cm<sup>3</sup>) and this solution was added slowly to the mixture. The mixture was heated to 50°C and the temperature maintained for 1h.

The mixture was allowed to cool and toluene (200cm<sup>3</sup>) was added to the flask. The solution was extracted with water (600cm<sup>3</sup>). The aqueous phase was back extracted with toluene (2 x 100cm<sup>3</sup>). The organic layers were combined and washed with water (2 x 100cm<sup>3</sup>), dried over MgSO<sub>4</sub> and filtered. The toluene was removed by evaporation under reduced pressure to yield a pale yellow oil (yield 38.5g, 98% based on trityl).

##### **STAGE 2**

Mono(trityl)tetraethyleneglycol (30g, 0.069mol), 4-toluenesulfonyl chloride (14.4g, 0.076mol) and dry tetrahydrofuran (50cm<sup>3</sup>) were placed in a 3 necked round bottom flask fitted with a thermometer and reflux condenser. The flask was placed in a dry-ice bath and the mixture allowed to cool to ~ -20°C. A solution of KOH (25.2g, 0.45mol) in water (100cm<sup>3</sup>) was added drop-wise over a period of 1h whilst maintaining the temperature at <0°C. Following the addition the reaction mixture was stirred for 1h whilst allowing the solution to warm to ambient.

The solution was extracted with diethylether ( $3 \times 150\text{cm}^3$ ). The ether layer was dried over  $\text{MgSO}_4$ , filtered and evaporated under reduced pressure. The solid was washed with MeOH and dried under vacuum (yield 34.3g, 85%).

### STAGE 3

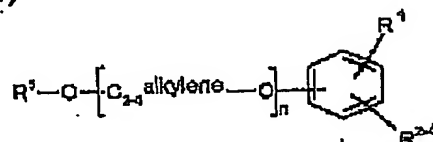
NaOMe (0.55g, 10.2mmol) was dissolved in the minimum amount of N,N-dimethylformamide (DMF) and added to 4-acetoxystyrene ( $1.3\text{cm}^3$ , 8.5mmol) contained in a round bottom flask. This solution was stirred at ambient for 45min then a solution of the tosyl derivative of mono(trityl)tetraethyleneglycol (5g, 8.5mmol) in DMF was added. The reaction was allowed to continue overnight at ambient.

The DMF was removed by evaporation under reduced pressure. The oil remaining was dissolved in isopropylacetate and extracted with water. The organic layers were combined, dried over  $\text{MgSO}_4$  and filtered. The solvent was removed by evaporation under reduced pressure to leave a pale yellow oil that crystallised on standing (yield 3.5g, 77%).

# CLAIMS

1. A monomer which comprises a protected hydroxypolyC<sub>2-4</sub> alkyleneoxy chain attached to a polymerisable unit wherein the protected hydroxypolyC<sub>2-4</sub> alkyleneoxy chain contains from 2 to 10 C<sub>2-4</sub> alkyleneoxy groups and wherein the hydroxypolyC<sub>2-4</sub> alkyleneoxy chain is protected with an optionally substituted trityl group.

2. A monomer of formula (1)



wherein

R<sup>1</sup> is an optionally substituted ethylene group;

R<sup>2-4</sup> are independently hydrogen, hydrocarbyl, halogen, or hydrocarbyloxy;

R<sup>5</sup> is an optionally substituted trityl group; and

n is 2 to 10.

3. A process for the preparation of a polymer support comprising polymerisation of a monomer comprising a protected hydroxypolyC<sub>2-4</sub> alkyleneoxy chain attached to a polymerisable unit wherein the protected hydroxypolyC<sub>2-4</sub> alkyleneoxy chain contains from 2 to 10 C<sub>2-4</sub> alkyleneoxy groups and wherein the hydroxypolyC<sub>2-4</sub> alkyleneoxy chain is protected with an optionally substituted trityl group, under conditions to produce cross-linking.

4. A polymer support which comprises protected hydroxypolyC<sub>2-4</sub> alkyleneoxy chains attached to a cross-linked polymer wherein the protected hydroxypolyC<sub>2-4</sub> alkyleneoxy chain contains from 2 to 10 C<sub>2-4</sub> alkyleneoxy groups and wherein the hydroxypolyC<sub>2-4</sub> alkyleneoxy chains are protected with an optionally substituted trityl group.

5. A polymer support obtainable by the process of Claim 3.

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